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Delirium and tremor associated with ertapenem treatment

Ertapenem tedavisine bağlı gelişen deliryum ve tremor

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Abstract

Though seizures are the most commonly reported neurotoxic adverse effects of ertapenem, there are numerous other side effects including hallucinations, disorientation, and tremors which are hardly ever reported. These side effects can be life-threatening, in the case of continued use of ertapenem. However, these treatment-related side effects completely resolve with discontinuation of the treatment. A 60-year-old female patient underwent hemodialysis owing to acute kidney insufficiency. Ertapenem was used to treat the condition since cultures from blood and urine sample of the patient showed growth of extended-spectrum beta-lactamase positive *Escherichia coli*. It was seen that the patient experienced tremors in the hand on the sixth day of the treatment, and hallucinations, disorientation, aggression, impaired speech as well as gait disturbances on the eighth day. With the discontinuation of ertapenem treatment, all these symptoms disappeared within 72 hours. This paper emphasizes on the neurotoxicity other than seizures resulting from ertapenem.

Keywords: ertapenem, delirium, tremor, hallucination.

Öz

Ertapeneme bağlı nörotoksik yan etkilerden nöbet sıklıkla bildirilmesine rağmen, halüsinasyon, dezoryantasyon, tremor gibi nöbet dışı yan etkiler nadiren bildirilmiştir. Bu yan etkiler ertapenem kullanılmasının devam etmesi durumunda hayatı tehdit edici boyutlara ulaşabildiği gibi, kesilmesi durumunda tamamen gerilemektedir. Altmış yaşında kadın hasta akut böbrek yetmezliği nedeniyle hemodiyalize girmiş, kan ve idrar kültüründe genişletilmiş spekrumlu beta laktamaz pozitif Escherichia coli üremesi nedeniyle ertapenem başlanmıştır. Ertapenem tedavisinin altıncı gününde ellerinde tremor ve sekizinci gününde halusinasyon, dezoryantasyon, saldırganlık, konuşma ve yürüme bozukluğu başlamış, tedavi kesildikten sonra 72 saat içinde tüm bulgular gerilemiştir. Ertapeneme bağlı nöbet dışı nörotoksisiteye dikkat çekmek amacıyla bu olgu bildirilmiştir.

Anahtar Sözcükler: *ertapenem, deliryum, tremor, halusinasyon.*

Introduction

Ertapenem is a broad-spectrum carbapenem antibiotic effective against gram positive and gram negative aerobic as well as anaerobic bacteria (1). Common adverse reactions (>5%) include nausea, headache, diarrhea, and local reactions related to infusion. Among the neurological and psychiatric adverse reactions, the incidence of seizures is 0.5%, while that of altered mental status such as agitation, disorientation, confusion, decreased mental acuity, somnolence and stupor ranges from 3.3 to 5.1% (2). Neurotoxicity other than seizures, associated with ertapenem is extremely rare (3).

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Herein, the authors present a case report of a patient in whom delirium and tremors associated with the use of ertapenem were seen, which however completely disappeared once the treatment was discontinued.

Case Report

A 60-year-old female patient was admitted to the intensive care unit owing to acute kidney insufficiency. Medical history of the patient revealed chronic obstructive pulmonary disease and a previous abdominal surgery to relieve an ileus. On physical examination, it was found that the patient was conscious, cooperative and orientated, having a body temperature of 36 °C and an arterial blood pressure of 120/80 mmHg. The other systems were found to be normal. The laboratory test results showed a leukocytic count of 13.3/μL (80% neutrophil, 12% lymphocyte, 6% monocyte); hemoglobin

(Hb) 13.3 g/dL; platelet count (PLT) 585/μL; urea 306 mg/dL; creatinine 5.96 mg/dL; sodium (Na) 127 mmol/L and C-reactive protein (CRP) 57 mg/L. Arterial blood gas analysis revealed pH 7.06; pCO_2 32 mmHg; $p0_2$ 58.8 mmHg and HCO_3 7.3. Urinalysis was found to be positive for nitrite and pyuria. The patient presented a history of hemodialysis. An empiric antibiotic therapy comprising of ceftriaxone 1 g twice daily was administered. The creatinine level decreased to 1.92 mg/dL. However, the sampling of blood and urine cultures of the patient revealed the growth of extended-spectrum beta-lactamase positive *Escherichia coli* and the patient was then transferred to the ward. The patient was administered intravenous ertapenem at a dose of 500 mg once daily. On the third day of the treatment, ertapenem dose was titrated up to 1 g once daily as the creatinine level further reduced (to 0.81 mg/dL). However, on the sixth day of the treatment, the patient suffered from tremors of the hand. Neurological examination revealed normal findings except for the presence of tremors. The patient also experienced hallucinations, disorientation, aggression, impaired speech, and gait disturbance on the eighth day. The laboratory test results revealed a neutrophilic count of 11.3/μL; Hg 8.9 g/dL; PLT 315/μL; Cr 0.66 mg/dL; albumin 2.7 g/dL; Na 138 mmol/L, and CRP 29 mg/L. The findings on cranial computed tomography (CT) and electroencephalography (EEG) were normal. The patient was diagnosed with delirium and was administered peroral haloperidol 0.5 mg three times daily; however, she did not show any clinical response. The patient was not administered any medications other than ertapenem at the time of onset of the symptoms. The levels of creatinine and electrolytes were found to be normal. Yet, due to the absence of a possible etiology for delirium other than ertapenem treatment, it was decided on the tenth day to discontinue the treatment. Subsequently, with the discontinuation of the treatment, all the symptoms disappeared within 72 hours.

Written informed consent was obtained from the patient for publishing the individual medical record.

Discussion

The incidence of neurotoxic adverse effects associated with ertapenem treatment varies from 3.3% to 5.1% in the literature (2). Though seizures are frequently reported, adverse effects other than seizures are rarely recorded (1). Carbapenems are associated with seizures due to structural similarity and receptor antagonism with ɣ-aminobutyric acid (GABA) (2). However, the role of GABA receptor antagonism in eliciting neurotoxicity other than seizures is still not clear (4). Table 1 shows records of 15 patients in whom neurotoxicity symptoms other than seizures have developed with the administration of ertapenem (1-9).

The Naranjo Adverse Drug Reaction Probability Scale recorded a score of 6 for the patient. Delirium and tremors were the adverse drug reactions *probably* associated with ertapenem treatment (10).

Neurotoxic side effects have mostly been reported in the elderly patients suffering from end-stage kidney insufficiency and disorders of the central nervous system (2,3). Among all the cases reported till date, nine patients had a chronic renal failure (CRF), two patients had an acute renal failure (ARF), and only four patients did not have any kidney insufficiency. The age of all these patients ranged between 42 and 85 years. Ertapenem must be administered at a dose of 1 g intravenously per day in patients with a glomerular filtration rate (GFR) of ≥30 and 500 mg intravenously per day in patients with a GFR of <30 (3). Considering a GFR of 28.9 mL/min calculated using the Cockcroft-Gault equation, the patient in the present case was administered ertapenem at a dose of 500 mg intravenously for the first three days, followed by 1 g due to increased GFR levels up to 69.9 mL/min. In the previously published case reports, one patient had a history of infarction and one patient had a history of spinal cord injury (4,7). Nevertheless, in the present case, the patient did not have a known central nervous system disorder. On the basis of the presence of delirium, cranial CT and EEG were performed, which revealed normal findings. Due to the fact that 95% of ertapenem binds to proteins, the low albumin levels have been reported to be a risk factor for neurotoxicity (3). In the present case, the patient had an albumin level of 2.7 during the onset of symptoms, which could be a risk factor for the development of neurotoxicity. Uricosuric drugs can also cause neurotoxicity, inhibiting renal excretion of ertapenem (3). However, the patient in the present case did not receive any uricosuric drugs.

A review of the reported cases has revealed that the symptoms of neurotoxicity appear within 3 to 14 days after the initiation of treatment with ertapenem and these symptoms disappear within two to fourteen days after the discontinuation of drug therapy. In the present case, the symptoms appeared on the sixth day following the initiation of treatment and disappeared three days after the discontinuation of the treatment.

In conclusion, although neurotoxic side effects other than seizures, seen on the administration of ertapenem are rare, yet they may be life-threatening in case the drug is continued. Similar cases reported by Apodaca et al.(2) and Duquaine et al.(4) required mechanical ventilation. Following the discontinuation of the drug on the basis of neurotoxic findings (which could be related to ertapenem treatment), all the symptoms disappeared in the patients. Nevertheless, it should be kept in mind that ertapenem treatment can cause side effects like hallucinations, disorientation, speech disorders, gait disorder, tremors, aggressive behavior, myoclonus, and nystagmus, other than seizures and the drug must be discontinued immediately as these symptoms appear.

Table-1. Patient Characteristics Reported in the Literature

Reference	Age/Sex	Comorbidities	Reason for treatment	Side effects	The day of starting the treatment / The number of days to resolve side effects	Naranjo score
1	54/M	Interstitial nephritis, DM	Diabetic foot infection	Delusion, visual hallucination, convulsion, nystagmus, myoclonus	5/10	probable
1	48/M	Depression	Osteomyelitis, prosthetic infection	Confusion, disorientation, visual and auditory hallucination	10/3	probable
2	42/F	Alcoholic cirrhosis, ARF	Cellulitis, myositis	Delusion, hallucination, agitation, disorientation, insomnia, confusion, Speech disorder	7/2	4 (possible)
3	85/F	Hypertensive heart disease, CRF, Asthma	Urinary tract infection	Visual hallucination, disorientation, insomnia, depression	7/2	6 (probable)
4	79/M	DM, HT, spinal cord injury	Sacral osteomyelitis	Delirium, speech disorder, myosis	7/2	* (highly probable)
4	70/M	Metastatic bladder carcinoma, small bowel obstruction, ARF	Prophylaxis for intra-abdominal infection	delirium	5/2	probable
5	71/M	Depression	Osteomyelitis	Visual hallucination, suicidal ideation, disorientation	14/3	6 (probable)
6	72/M	CRF	Hernioplasty (prophylactic use)	Disorientation, aggression, unrest, visual hallucination, meaningless speech	5/7	*
6	79/F	CRF	Small bowel obstruction	Aggression, confusion, visual hallucination	3/7	*
6	73/F	CRF	Cellulitis	Confusion, visual hallucination, soliloquy	7/8	*
6	78/F	CRF	Acute cholecystitis	Hallucination, asterixis, myoclonic jerks, cognitive impairment	4/14	*
6	70/F	CRF	AV fistula infection	Hallucination, asterixis, myoclonic jerks, cognitive impairment	5/14	*
7	84/F	HT, CRF, previous cranial infarction	Urinary tract infection	Visual hallucination, confusion, meaningless speech	7/4	6 (probable)
8	58/M	Celiac disease, osteoporosis, chronic liver disease	Wound infection (hip)	Visual hallucination, confusion	14/2	*
9	61/M	CRF	Septic arthritis, prosthetic infection	Visual and tactile hallucination, generalized flinging movement	3/2	*

ARF (acute renal failure); CRF (chronic renal failure); DM (diabetes mellitus); HT (hypertension), * not reported

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